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Exercise and the regulation of energy intake

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Energy balance is the resultant of ingested calories and energy expenditure and is generally maintained within narrow limits over prolonged periods. Exercise leads to an increase in energy expenditure which is, in the long-term, counteracted by increased energy intake. Evidence for this comes from a study in voluntarily running female rats that increased their daily food intake to 130% of the sedentary controls. In contrast, when considered on a short-term basis, exercise will suppress food intake to prevent a potentially dangerous disruption of energy substrate homeostasis. Studies in permanently cannulated rats submitted to a test meal and 2 hrs swimming reveal that both food intake and exercise lead to increases in glucose and free fatty acid (FFA) levels in the blood. These changes in glucose and FFA, combined with the exercise-induced alteration in among others glucagon, corticotropin releasing hormone (CRH) and body temperature, may lead to the short-term anorexic effect of exercise.

Keywords: food intake; glucose; fatty acids; insulin; CRH eating paradox

Introduction

Energy balance is the result of ingested calories and energy expenditure and is generally maintained within narrow limits over prolonged periods. Exercise leads to an increase in energy expenditure and, therefore, to a negative energy balance. The following paragraphs focus on the effects of exercise on food intake. As a working hypothesis we assume that the negative energy balance following exercise will be counteracted by increased food intake, thereby ignoring possible effects of exercise on baseline temperature and resting metabolic rate, that is, issues that are beyond the scope of this review

Exercise and food intake

A simple experiment was performed to test the hypothesis that increased energy expenditure is followed by increased energy intake. Rats will voluntarily exercise in running wheels, when given the opportunity. In standard laboratory conditions, rats run in the wheels in the night, their active period. According to the hypothesis, running rats should maintain their body weight at a constant level similar to that of their sedentary littermates, simply because they will increase their caloric intake to compensate for the increased energy expenditure. Figure 1 presents the data for daily food intake and body weight of two groups of female rats: a sedentary group that was housed in standard rat cages, and a running group that was housed in similar cages but also had voluntary access to a running wheel. In the sedentary group food intake remained constant at approximately 16 g/d during the experimental period of 4 weeks. Running rats increased their food intake to about 130% of their baseline intake. No differences in body weight were observed between the two groups. These data show that in a comparison between sedentary and 'normally' active rats, exercise on a long term basis leads to a significant increase in food intake with no change in body weight, thus confirming the hypothesis.

A reduction in food intake after short-term exercise

The effects of exercise on food intake and body weight have been widely studied in humans and laboratory animals. A typical example is the study in exercising men and women by Staten.[1]. In this study, it was found that men did increase their energy intake during a 5 day training period which basically confirms our hypothesis. However, the increase in food intake was not sufficient to compensate for the caloric costs of exercise. Moreover, women did not change their food intake in the exercise period at all. Similar conflicting data have been observed.[2] A certain variability in the data may be expected due to

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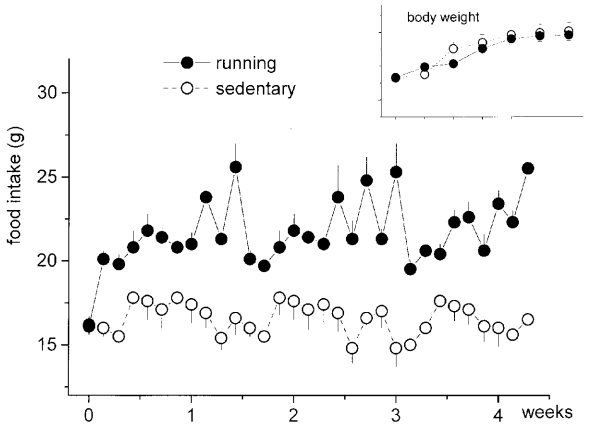

Figure 1 Daily food intake and weekly body weight for two groups of female rats: a sedentary group that was housed in standard rat cages and a running group that was housed in similar cages but also had voluntary access to a running wheel.

substantial differences in the experimental protocols—species, type of exercise, intensity, duration, environmental conditions, sex, and age. In humans, factors such as learning, restrained eating, social environment, peer pressure will also play a role. Still, it is remarkable that the majority of the studies dealing with exercise and food intake report a *reduction* in energy intake, especially after short-term exercise.

Larue-Achagiotis *et al*[3] in their studies on rats, claim that the unexpected decrease in food intake after exercise might, in part, be due to a variability in the diet composition. They showed that rats starved for a long time and refed with a self-selection regimen were hyperphagic on the first day of refeeding[4] while rats refed with a complete chow diet manifested post-starvation anorexia.[5–7] This could be explained by the fact that self-selecting rats had the opportunity to choose one particularly needed (that is metabolizable) nutrient, whereas the chow fed rats were forced to ingest the high-carbohydrate lab chow diet that they were unable to metabolize at the beginning of refeeding. It is tenable that an analogous phenomenon may occur in the postexercise period, although the crucial experiment in which the effects of exercise on food intake in self-selecting and chow fed rats are studied remains to be done.

Limitations of the laboratory diet may therefore partly explain the unexpected reduction in energy intake after exercise. However, this explanation does not apply for human studies. Humans also showed a reduction in energy intake after exercise with no compensatory intake on the following days.[8,9] The group of King and Blundell extensively studied this phenomenon of exercise-induced anorexia in humans. Subjective feelings of hunger were significantly suppressed during and immediately after exercise. Intense exercise also delayed the start of eating of a post-exercise meal although it had no effect on the amount of food consumed.[8,9,10] Body weight remained unchanged in these studies despite the reduction in food intake, suggesting that energy balance may have been restored by mechanisms independent of food intake such as decreased energy expenditure.

The eating paradox by Steve Woods

Exercise induces short-term anorexia that is characterized by a brief suppression of hunger, accompanied by a delay of the onset of eating. In other words, the increased energy expenditure during exercise is accompanied by a reduction in food intake, a finding which is seemingly in conflict with the theory of homeostasis in organisms. However, it may not be such a contradiction at all. One may argue that for homeostatic reasons, increased endogenous energy mobilization during exercise should have an inhibitory influence on food intake.

In 1991, Stephen C. Woods published a theory called 'The eating paradox: how we tolerate food'.[11] Woods made the point that food, although necessary for the provision of energy, provides a potential threat to organisms, including humans. He stated that eating is a particularly stressful event in a homeostatic sense, because during and after a meal, digested fuels are absorbed into the blood and this will markedly disrupt energy homeostasis. Hence, elevated fuels in the blood (at least at a chronic basis) are associated with many metabolic abnormalities, including obesity, syndrome X and several cardiovascular disorders. Acute elevations of glucose and fatty acid may cause alterations in many central nervous system neurotransmitter systems.[12,13] This may also explain why a meal is limited (a phenomenon that is called satiety): to prevent an uncontrolled rise in fuels when a meal is eaten. Further evidence for the idea that eating may resemble certain aspects of a potential stress situation of the body is provided by the finding that 'stress' hormones such as catecholamines, adrenocorticotropic hormone (ACTH) and corticosterone become elevated during a meal.[14–16] Therefore, the act of eating is—in an endocrine sense—stressful for an organism.

To prevent the unwanted 'side-effects' of food intake, the body immediately responds to the onset of a meal by accelerating all the processes that remove the elevated fuels from the blood, thus helping homeostatically to preserve normal blood fuel levels Figure 2). In fact, some of these mechanisms occur even before the intake of a spontaneous meal.[17] The hormone insulin, released by the B-cells of the endocrine pancreas during an increase in glucose, fatty acids or amino acids, plays an important role in this process since it facilitates the uptake of these energy substrates by most tissues. Even the consumption of energy is stimulated during a meal (dietary or

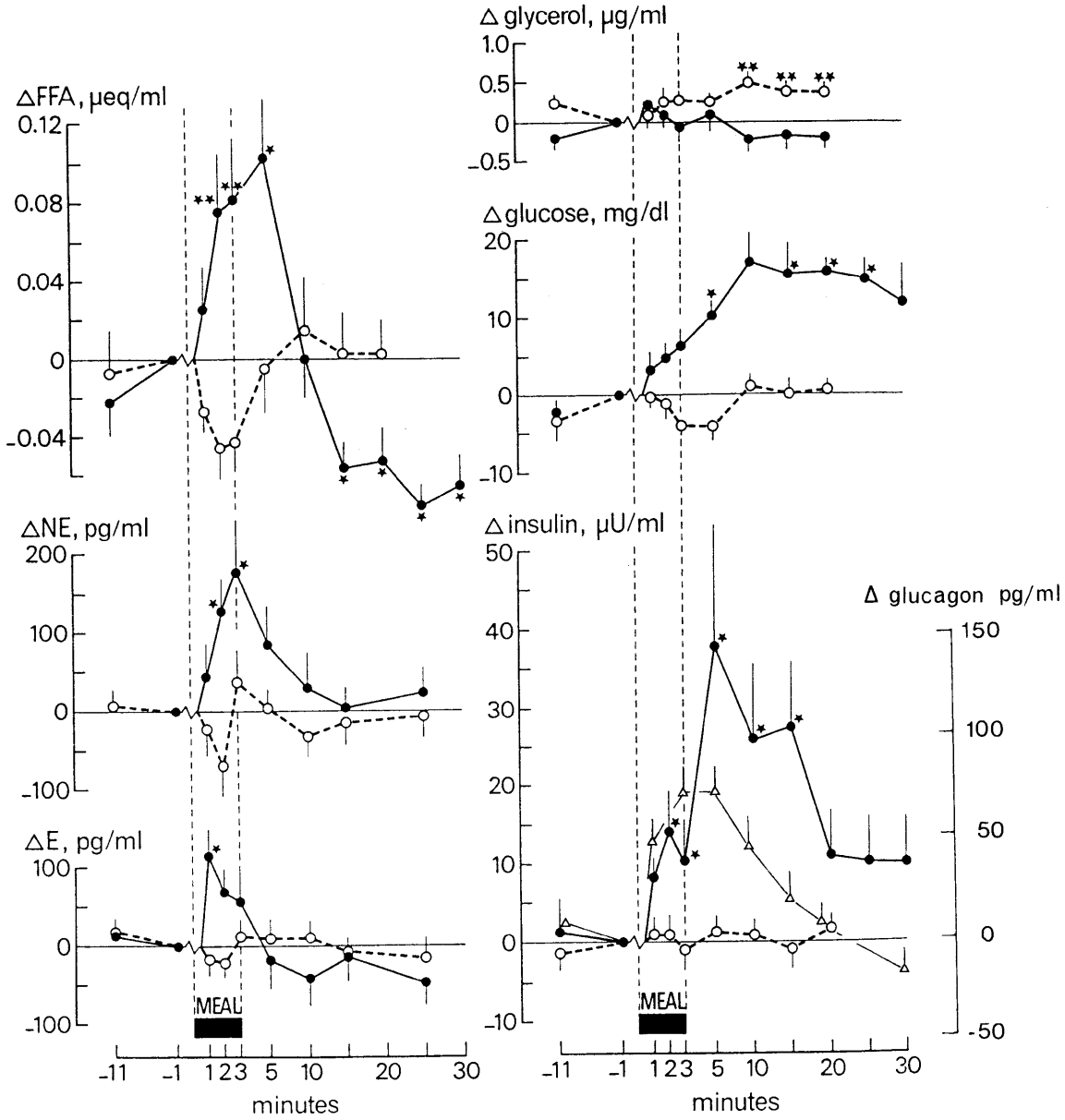

Figure 2 Metabolic and hormonal consequences of food intake: meal-induced changes in blood glucose and plasma free fatty acids (FFA), glycerol, glucagon and adrenaline (E) and noradrenaline (NE) (modified from 16).

meal-induced thermogenesis), which can be seen as a mechanism to burn excess ingested energy.

Exercise and the eating paradox

According to Woods,[11] the post-meal period is one of especial risk considering that there is potential danger to having elevated levels of fuels in the blood. Because of this, any behavior that causes the mobilization of endogenous fuels into the blood should be reduced or inhibited at this time. Exercise is associated with sympathetic activation and fuel mobilization which might explain the generally accepted view that one should not perform vigorous exercise immediately after a meal.

The converse of the preceding argument is that if endogenous fuels have been mobilized because of acute metabolic needs, feeding should be simultaneously inhibited so that fuel levels in the blood do not attain higher levels.[11] Consequently eating should be inhibited during and after exercise, since exercise is a situation that involves the mobilization of stored fuels into the blood. In fact, any situation that involves fuel mobilization would have to inhibit food intake. Indeed, stressors that activate sympathoadrenal system and/or the hypothalamic-pituitary axis (and consequently increase blood glucose and free fatty acids (FFA) levels) are known to cause a decrease of food intake. Administration of the stress hormones has the same effect. According to Woods' eating paradox,[11] the point is that food intake requires a metabolically 'safe' interval when the impact of the meal is likely to be minimal.

Energy substrate homeostasis during exercise

The use of chronic indwelling intravenous catheters makes it possible to monitor the exercise-induced changes in the hormonal and metabolic factors that may be involved in short-term suppression of food intake. Rats were equipped with a permanent catheter and were then trained to exercise for 2 h per d. Exercise consisted of strenuous swimming against a counter current in a pool filled with water of 33°C. Figure 3A presents the blood glucose and plasma FFA levels that were measured during a 2-h swimming session after two weeks of training. After the onset of exercise, blood glucose increased to a level that was about 15% above baseline and remained at that level during the whole swimming period. Plasma levels of FFA gradually increased over the course of the experiment towards a level that was about twice baseline values. Glucose and FFA remained elevated after the termination of exercise which, according to the eating paradox, may explain the post-exercise suppression of food intake.

The mechanisms by which these elevated levels of circulating glucose and FFA may suppress feeding behavior are relatively unknown. The current opinion is that glucose may activate glucosensors in the liver/hepatic portal vein area leading to a reduction in food intake through a vagal afferent pathway.[18] Evidence for this comes from studies that have shown that systemic glucose infusion reduces food intake, in particular when glucose is infused into the portal vein.[19–21] Furthermore, glucosensitive neurons located in areas in the brain stem (NTS) and the hypothalamus seem to be involved in the central nervous system network that senses glucose availability and controls glucose homeostasis and food intake.[18,22] Evidence for a satiety effect of fatty acids comes from the findings that intraduodenal as well as intravenous infusion of lipids reduces food intake[23,24] and that administration of fatty acid oxidation blockers such as mercaptoacetate and methyl palmoxirate lead to increased food intake.[25,26] The sensors for this satiating effect of FFA are probably located in the liver, since hepatic vagotomy markedly attenuates lipoprivation-induced eating.[26,27] Studies from the group of Ritter revealed that elevated plasma FFA levels may suppress eating through a vagally mediated sensory mechanism acting on food intake regulating areas in the brain such as the area postrema/NTS and the lateral parabrachial nucleus.[28]

Lactate may also serve as a short-term satiety factor during and immediately after exercise. Figure 4 presents the glucose, FFA and lactate levels in rats exercising for 20 min.[29] Note that both glucose and FFA remained elevated above baseline until the end of the experiment which is more than 90 min after the termination of this short-term exercise. The most

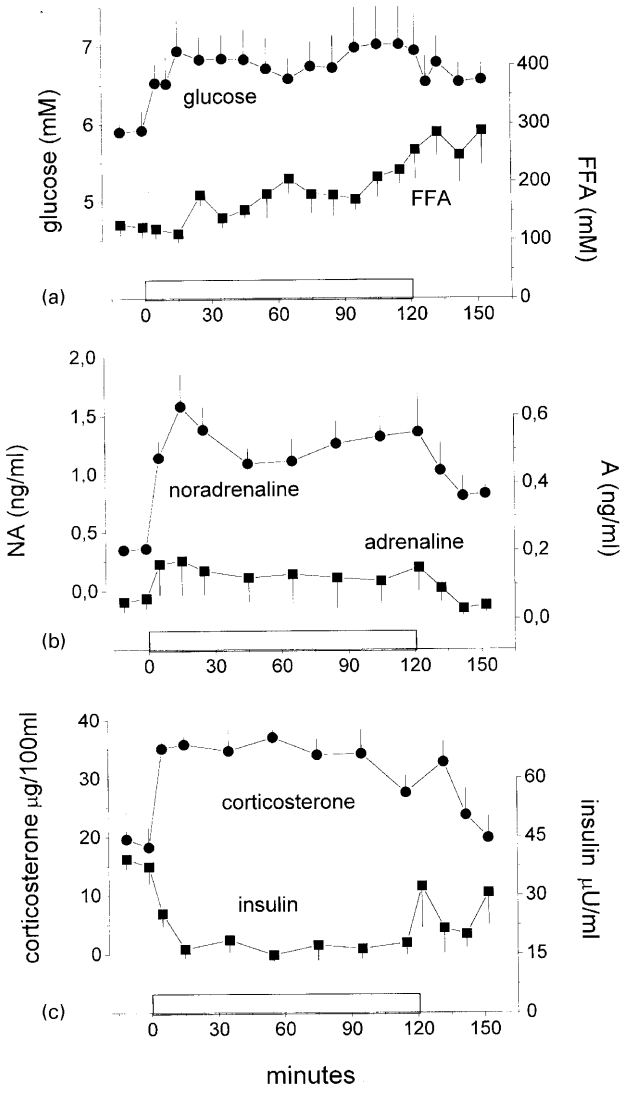

Figure 3 Metabolic and hormonal consequences of exercise: swimming-induced changes in blood glucose and plasma free fatty acids (FFA) 3a, adrenaline (A), and noradrenaline (NA) 3b, corticosterone and insulin 3c. Exercise consisted of 120 min of swimming indicated by horizontal bar.

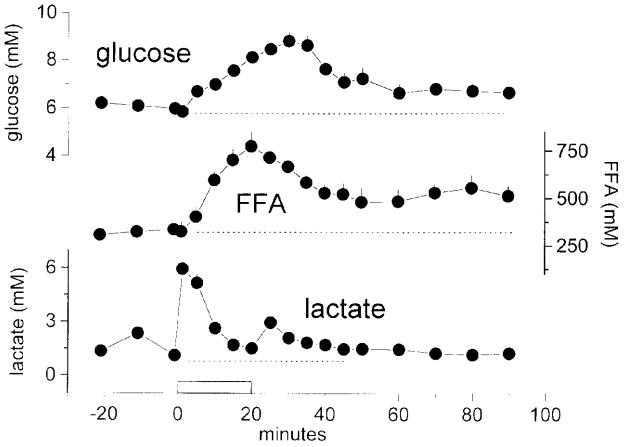

Figure 4 Metabolic consequences of short term exercise: changes in blood glucose and plasma free fatty acids (FFA) and lactate before, during and after swimming. Exercise consisted of 20 min of swimming indicated by horizontal bar (modified from 29).

important finding of this study is that plasma lactate levels are also increased during and after exercise. Data in literature reveal that administration of lactate also inhibits food intake and this hypophagic effect of lactate is dependent on intact hepatic vagal afferents, once again pointing to the liver as the main candidate for a sensory function involved the regulation of food intake by blood-borne nutrients.[30,31]

The contribution of other energy substrates such as glycerol, amino acids and ketone bodies are probably of minor importance for the interactions between exercise and food intake. Still, they cannot be totally excluded since most of these components are increased during exercise and are known to be shunted into the common metabolic pathways. Indeed, some of them suppress food intake when injected systemically.[18]

Hormonal changes during exercise and food intake

Changes in plasma hormone levels may also contribute to the short-term satiety effect of exercise. In the 2-h swimming study, we found that exercise is accompanied by an increase in the release of glucagon, a hormone from the endocrine pancreas. Glucagon suppresses food intake (independent of its effects on glucose homeostasis), especially in combination with other satiety factors such as cholecystokinin (CCK) and serotonin (5-HT).[32] Data on exercise-induced changes of CCK and 5-HT are, unfortunately, scarce. The same is true for corticotropine releasing hormone (CRH), a centrally acting hormone that may serve as another candidate for the short-term suppressive effect of exercise on energy intake. The anorexic effect of CRH is well documented and, according to Richard,[33] CRH is increased during treadmill running. Richard *et al*[34] also showed that administration of a CRH-antagonist prevented the anorexic effect of an acute session of exercise.[34] Furthermore, the involvement of CRH in the anorexic effects of exercise is consistent with the observation that exercise preferentially suppresses the intake of dietary fat.[6,35]

Plasma noradrenaline levels, reflecting an increased outflow of NA from the peripheral nerve endings of the sympathetic nervous system, are also increased during exercise (Figure 3B). Sympathetic NA has probably no direct actions on food intake. However, indirect actions of NA on peripheral metabolism such as increased lipolysis, brown adipose tissue thermogenesis and glycogenolysis in liver are all known to be involved in the suppression of energy intake. In our experimental set-up, no changes were found in the levels of adrenaline (A) during exercise (Figure 3B), indicating that the amount of emotional stress in the swimming model is relatively limited.[36]

Hormonal changes during exercise and body weight maintenance

Leptin, a hormone released by white adipose tissue, and insulin, the glucoregulatory hormone from the endocrine pancreas, are known to be involved in the regulation of food intake and body weight.[37] Both hormones bind to discrete receptors on neurons located in brain areas involved in the regulation of food intake and local infusion of small amounts of insulin as well as leptin into these brain areas produces long-lasting reductions in food intake. Both hormones however, obey kinetics of receptor-mediated transport (located at the level of the blood-brain barrier) before entering the brain.[38,39] This principally yields these hormones unfavorable to transmit rapid fluctuations in circulating levels to be passed on to brain. It is therefore unlikely that leptin and insulin are involved in the direct effects of exercise on eating behavior. Figure 3C shows that insulin levels are lower in exercising individuals. Also leptin levels are lower in exercising individuals.[40] In the long-term, exercise-induced reductions in insulin and leptin could potentially reduce hypothalamic CRH and this may explain the compensatory increase in food intake seen in the long-term exercise studies.

Corticosterone levels are also changed during and after exercise (Figure 3C). Corticosteron (or cortisol in several other species) increases food intake on a long-term basis.[41] It is therefore tenable that, like leptin and insulin, the exercise-induced increase in corticosterone may have contributed to the compensatory increase in food intake in long-term exercise studies.

Long-term versus short-term homeostatic mechanisms

In conclusion, there are a number of differences between short-term and long-term effects of exercise on food intake. First, exercise is associated with several metabolic and hormonal changes that will instantaneously inhibit food intake to prevent a too dramatic and potentially dangerous alteration in energy substrate (and possibly also temperature) homeostasis. Second, an exercise-induced increase in energy expenditure is counteracted by a compensatory increase in energy intake in the long-term. The latter confirms the leading hypothesis that energy balance is generally maintained within narrow limits over prolonged periods. Not all studies in which animals are forced to exercise over longer periods may fulfill this criterion. Baseline measurements of plasma adrenaline and/or corticosterone/cortisol levels may reveal that these studies are measuring the effects of chronic stress (leading to chronically elevated levels of

hypothalamic CRH) rather than long-term effects of exercise on energy balance.

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